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American Chemistry* Council Good Chemistry Maker It Possible

November 9, 2000

Carol Browner, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22 116
Attention: Chemical Right-to-Know Program

Jessica T. Sandler, MHS
Federal Agency Liaison
People for the Ethical Treatment of Animals
4800 Baseline Road, #E104-390
Boulder, CO 80305

Re: Response to Comments on Test Plan

Dear Ms. Browner and Ms. Sandler:

This letter is submitted by the American Chemistry Council Olefins Panel (Panel) to respond to comments it has received on its test plan and robust summaries for the Crude Butadiene C4 category. Comments were received from the Environmental Protection Agency (EPA) and People for the Ethical Treatment of Animals (PETA).

General Comments and Response

The Panel appreciates EPA's recognition that the Panel supplied a complete package that constituted an acceptable category submission and test plan overall. The Panel also appreciates PETA's recognition that the Panel has formed an appropriate chemical category and is taking appropriate steps to coordinate with the efforts of other industry groups which are addressing related chemical categories.

PETA has raised a number of questions concerning the necessity of the proposed testing. The Panel takes these comments seriously, and agrees with the principles PETA cites from EPA's October 14, 1999 letter, namely that: (1) in analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach; and (2) before generating new information, participants in the HPV program should consider whether any additional information obtained would be useful or relevant. In this case, however, the Panel believes it has achieved an appropriate balance between identified data gaps and animal welfare concerns.

As the Panel develops test plans for additional chemical categories, the Panel will apply thoughtful, qualitative analyses in lieu of a rote checklist approach, and will make every reasonable effort to avoid unnecessary use of laboratory animals.

Suggestion to Eliminate the Acute Inhalation Test

Both EPA and PETA have recommended against the conduct of an acute inhalation (LC_{50}) test. The Panel agrees with this recommendation and the supporting rationales presented by EPA and PETA, and accordingly will delete this study from the test plan. Moreover, the Panel will not include an acute inhalation study in future test plans for other olefins categories absent some unique justification not present in this case.

Other EPA Comments

EPA has presented several other specific comments. Most of these will be addressed in the Panel's final report for this test plan. We address here one specific comment: EPA's suggestion that the Panel consider conducting the *in vivo* health effects studies in mice, not rats, based on available studies of 1,3-butadiene that show that the mouse is the more sensitive species based on exposure concentrations.

The Panel has considered this comment, and has decided to conduct the OECD Guideline Number 422 study (combined repeated dose/reproductive and developmental effects/neurotoxicity screen) in the rat for several reasons. First, the OECD 422 study was designed for the rat and the standard test protocol specifies the rat as the test species. Second, because the rat is the usual test species for this study, an extensive historical control database exists for the rat. We are not aware of a comparable historical control database for the mouse. Third, for approximately equivalent exposure concentrations of 1,3-butadiene by inhalation, the metabolic profile in rats and mice is remarkably different. Rats form much less of the diepoxide metabolite than mice, and mechanistic studies show that the diepoxide metabolite is obligatory for ovarian atrophy. Fourth, extensive *in vitro* and *in vivo* metabolic studies in mice, rats and human tissues, shows that the metabolic profile of butadiene in humans is more similar to rats than it is to mice. Selection of the mouse as the "most sensitive" species is inappropriate because of its documented unique metabolic status. The Panel believes the rat is the more appropriate test species for the combined repeated dose/reproductive and developmental effects/neurotoxicity screen, in general, and specifically for process streams containing butadiene. The application of the rat as the test species based on available scientific data is expected to provide an assessment of risk more realistically relevant to humans.

In the case of the micronucleus test (OECD Guideline Number 474), where the mouse is the usual test species, the Panel will use the mouse. The Panel believes the mouse is scientifically appropriate because the purpose of the test is to determine the genotoxicity potential of streams containing butadiene, the mouse is the

usual test species for this test, and butadiene does not cause an effect *in vitro* or in a rat micronucleus test. The Panel views the mouse micronucleus test as a mechanistic test, rather than a test to determine potential risk to humans; thus, the use of an overly sensitive test species is not inappropriate.

In summary, the Panel has considered the choice of test species and does plan to use the standard test protocol and standard test species for each mammalian test conducted on Group 1 test streams.

The Panel appreciates the comments it has received from EPA and PETA. Any comments or questions concerning this letter may be directed to Elizabeth J. Moran, Manager of the Olefins Panel, at (301) 924-2006, or via email at Elizabeth_Moran@americanchemistry.com.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR